Exhibit C:
Copy of Development Protocol

DEVELOPMENT PROTOCOL

Protocol to Study the Effect of Sterilisation Temperature on Budesonide Concentrates

Document Reference:	**D067 (Version 01)**
Date of Issue:	[redacted]
Supersedes:	**N/A**
Page:	**1 of 9**

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1.0 Introduction

This study is designed to investigate the effect of sterilisation temperature on Budesonide concentrated suspensions.

A previous study, 'The effect of sterilisation temperature on Budesonide concentrate and the effect of temperature cycling on Budesonide raw material', detailed in protocol D063, has been completed and will be reported along with this study.

This study will involve assessing the effects of the following variables; Budesonide concentration, Polysorbate 80 concentration, autoclave holding time and autoclave temperature on the physical and chemical degradation of concentrated Budesonide suspensions.

2.0 Experimental

2.1 Preparation of Concentrated Suspensions

Prepare four 500 mL concentrated Budesonide suspensions, according to the method referenced in LB087 p169, and label them A, B, C and D. The formulation of the samples is detailed in Table 1. Concentrated suspensions A and B contain 5% of the total Polysorbate 80 that will be present upon dilution to form the final product suspension. Concentrated suspensions C and D contain 100% of the total Polysorbate 80 that will be present upon dilution to form the final product suspension.

Table 1: Formulation of Concentrated Budesonide Suspensions (ref Lab book LB137 p4)

	Concentration (mg / mL)		Weight needed for 500 mL batch (g)	
Budesonide	A	37.5	A	18.75
	B	75	B	37.5
	C	75	C	37.5
	D	150	D	75
Polysorbate 80 Ph. Eur.	A	0.75	A	0.375
	B	1.5	B	0.75
	C	30	C	15
	D	60	D	30
Sodium Chloride Ph. Eur.	8.5		4.25	
Sodium Citrate Dihydrate Ph. Eur.	0.5		0.25	
Citric Acid Monohydrate Ph. Eur.	0.31		0.155	
Disodium Edetate Dihydrate Ph. Eur.	0.1		0.05	

2.2 Sterilisation Temperature Studies

From each of the concentrated suspensions A and B partition eight samples into individual pre-made stainless steel vessels (with a tri-clover blank connection at one end, and the other closed) dimensions, approximately 25 mm x 150 mm. From each of the concentrated suspensions C and D partition four samples into individual pre-made stainless steel vessels (with a tri-clover blank connection at one end, and the other closed) dimensions, approximately 25 mm x 150 mm. All samples should be approximately 50 mL of concentrated suspension.

Label the eight samples prepared from concentrated suspension A as samples A1, A2, A3, A4, A5, A6, A7 and A8.
Label the eight samples prepared from concentrated suspension B as samples B1, B2, B3, B4, B5, B6, B7 and B8.
Label the four samples prepared from concentrated suspension C as samples C1, C2, C3 and C4.
Label the four samples prepared from concentrated suspension D as samples D1, D2, D3 and D4.

Heat the sample containers in an autoclave set to the holding temperatures detailed in Table 2. After heating, allow the vessels to cool to room temperature before opening.

Table 2: Autoclave conditions

Sample	Autoclave Holding Temperature (^{o}C)	Autoclave Holding Time (min)
A1	Control	Control
A2	Control	Control
A3	110	120
A4	110	120
A5	121	20
A6	121	20
A7	121	30
A8	121	30
B1	Control	Control
B2	Control	Control
B3	110	120
B4	110	120
B5	121	20
B6	121	20

Table 2 cont.

Sample	Autoclave Holding Temperature (°C)	Autoclave Holding Time (min)
B7	121	30
B8	121	30
C1	Control	Control
C2	Control	Control
C3	121	20
C4	121	20
D1	Control	Control
D2	Control	Control
D3	121	20
D4	121	20

* Control samples will be stored at room temperature, i.e. will not be placed into the autoclave.

2.3 Preparation for Analysis

2.3.1 Samples A1 to A8

Vigorously shake each sample. Prepare samples for assay as detailed in section 2.4.

To prepare samples for particle size analysis, shake each sample and dilute to 0.5 mg/mL as outlined below. This step is the preparation of material equivalent to the finished product. For each sample take 3.333 g of sample and dilute to 250 mL with bulk excipient solution with the formulation detailed in Table 3.

Table 3: Formulation of placebo for samples A1 to A8 (ref. Lab book LB137 p06)

	Concentration (g / L)
Polysorbate 80 Ph. Eur.	0.193
Sodium Chloride Ph. Eur.	8.5
Sodium Citrate Dihydrate Ph. Eur.	0.5
Citric Acid Monohydrate Ph. Eur.	0.31
Disodium Edetate Dihydrate Ph. Eur.	0.1
Water for HPLC	To 1 L

2.3.2 Samples B1 to B8

Vigorously shake each sample. Prepare samples for assay as detailed in section 2.4.

To prepare samples for particle size analysis, shake each sample and dilute to 0.5 mg/mL as outlined below. This step is the preparation of material equivalent to the finished product. For each sample take 1.667 g of sample and dilute to 250 mL with bulk excipient solution with the formulation detailed in Table 4.

Table 4: Formulation of placebo for samples B1 to B8 (ref. Lab book LB137 p06)

	Concentration (g / L)
Polysorbate 80 Ph. Eur.	0.191
Sodium Chloride Ph. Eur.	8.5
Sodium Citrate Dihydrate Ph. Eur.	0.5
Citric Acid Monohydrate Ph. Eur.	0.31
Disodium Edetate Dihydrate Ph. Eur.	0.1
Water for HPLC	To 1 L

2.3.3 Samples C1 to C4

Vigorously shake each sample. Prepare samples for assay as detailed in section 2.4.

To prepare samples for particle size analysis, shake each sample and dilute to 0.5 mg/mL as outlined below. This step is the preparation of material equivalent to the finished product. For each sample take 1.333 g of sample and dilute to 200 mL with bulk excipient solution with the formulation detailed in Table 5.

2.3.4 Samples D1 to D4

Vigorously shake each sample. Prepare samples for assay as detailed in section 2.4.

To prepare samples for particle size analysis, shake each sample and dilute to 0.5 mg/mL as outlined below. This step is the preparation of material equivalent to the finished product. For each sample take 0.667 g of sample and dilute to 200 mL with bulk excipient solution with the formulation detailed in Table 5.

Table 5: Formulation of placebo for samples C1 to C4 and D1 to D4 (ref. Lab book LB137 p06)

	Concentration (g / L)
Polysorbate 80 Ph. Eur.	0
Sodium Chloride Ph. Eur.	8.5
Sodium Citrate Dihydrate Ph. Eur.	0.5
Citric Acid Monohydrate Ph. Eur.	0.31
Disodium Edetate Dihydrate Ph. Eur.	0.1
Water for HPLC	To 1 L

2.4 Analysis

Analyse each sample using the following tests and methods:

- Budesonide content – DTM003
- Budesonide degradants/impurities – DTM003
- Content Epimer A – DTM003

Note: deviation from DTM003

Sample Preparation

Assay samples are prepared directly from the concentrate. A weight of sample (see below) is accurately weighted into a 200.0 mL volumetric flask using a pipette. Dissolve in 30 mL of acetonitrile (HPLC Grade), then make to volume with water (HPLC Grade).

37.5 mg/mL Concentrate (A) - 0.533g

75 mg/mL Concentrate (B and C) - 0.266g

150 mg/mL Concentrate (D)- 0.133g

- Appearance of suspension – DTM001
- Particle size – DTM045 (updated method detailed in LB083 p114-115).

3. Treatment of Results

Compare the results generated against the proposed specification for Budesonide Inhalation Suspension (see Appendix 1) and the Innovator product profile.

Appendix 1 - Proposed Specification for Budesonide Inhalation Suspension

Parameter	Reference	Product Specification	
Appearance of Solution	DTM001	A clear solution, after shaking a white suspension.	
Odour of Suspension	DTM001	Practically Odourless	
Colour of Suspension	DTM001	A Fine Opaque, Off White Suspension.	
Particle Size	DTM045	Report Result	
Budesonide Identity	DTM003	HPLC Retention Time within ± 5% of Standard	
Budesonide Content 0.25 mg/ml 0.50 mg/ml	DTM003	 0.2375 – 0.2625 mg/ml 0.4750 – 0.5250 mg/ml	
Content of Epimer A	DTM003	45.0 – 49.0%	
Budesonide Degradants/impurities	DTM003	Desonide 16α-hydroxypredinisolone 21-dehydro-budesonide Budesonide 1,2 dihydro 22-Methyl homologue D-homobudesonide 14,15-dehydrobudesonide S-11-Keto budesonide R-11-Keto budesonide S- 21 – Acetate budesonide R – 21 – Acetate budesonide Maximum individual unknown Total Impurities	≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.2% wrt active. ≤ 0.1% wrt active. ≤ 1.5% wrt active.